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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,724	08/31/2001	Xu Cao	D6106D	2798

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EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,724	CAO ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All objections and rejections not repeated in the instant Action have been withdrawn due to applicant's response to the previous Action.

Claim Rejections - 35 USC § 112

Claims 1 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record set forth in the paper mailed 10/22/03 (repeated below, slightly modified as necessitated by the applicant's amendment filed 6/1/04). Applicants' arguments filed 6/1/04 have been fully considered but they are not deemed to be persuasive.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art,

the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claim. The most relevant Wands factors for evaluating the enablement of the instant rejection are discussed below.

1. Nature of the invention. The claimed invention is drawn to a method of stimulating bone formation in an individual comprising inducing an interaction between Smad1 and a homeobox-containing transcription factor (elected Hoxc-8) by over-expressing Smad1, wherein said interaction induces a BMP-responsive gene (elected osteopontin) which produces osteoblast and/or chrondroblast differentiation thereby stimulating bone formation. The claimed method reads on any method of overexpression of Smad1, including overexpression by gene therapy methods to add an overexpressing Smad1 gene or to mutate the endogenous Smad1 gene to overexpress, and administration of compounds that cause overexpression of Smad1 (e.g., specific antisense molecules). The claimed invention is very broad encompassing many very different methods with only the target, increasing the claimed interaction by overexpressing Smad1, in common. The claimed invention thus is very complex, especially

since the invention is used to treat various complex, unspecified bone diseases.

2. Unpredictability of the art. The arts of stimulating bone formation in an individual and regulating disease (the only way of using the claimed method) are unpredictable. The ability to target an inducing DNA or drug with the specificity required, in the instant case, such that only bone matrix gene expression is induced, and only in bone tissue, has not been demonstrated and is highly unpredictable. The specification must teach one skilled in the art how to make and use an invention without undue experimentation. The regulation at issue requires engagement of cellular receptors and phosphorylation of receptor associated signal transduction proteins (Smads) which subsequently translocate to the nucleus. In the nucleus, such proteins de-repress gene transcription through specific interaction with homeobox-containing transcription factors (Hoxc-8). Without a complete definition of the cell types expressing the appropriate Smad protein and Hox protein, and specific targeting of those cells by the agents that overexpress Smad1 as claimed, one would expect that the agents would not reach the target cells in an effective concentration given that the vast majority of cells in the individual are not bone-generating cells. One must conclude that the arts of

stimulating bone formation and using it to regulate diseases in individuals are unpredictable, for even one of the methods encompassed by the claimed invention, let alone the broad scope, drawn to very different methods, encompassed by the claims.

Caldwell is cited to show the unpredictability in the art concerning how to make and use a drug based upon a compound with a demonstrated in vitro activity. Caldwell teaches that drug action is the result of interaction with target sites, for both desired and undesired actions, modulated by the transfer processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters and leaves the body. This reference teaches that there is far more inter- and intraspecies variation, in animals and humans, in the factors influencing the nature and extent of internal exposure, than in the sensitivity of drug targets and this pharmacokinetic variability is the cause of major problems in drug development. Caldwell also teaches that failure to take these pharmacokinetic defects, including poor absorption, very short or very long half-life, enzyme induction and high first pass effect, into consideration can cause expensive delay and/or failure during development. This reference thus shows that drug development is very unpredictable, requiring the consideration of many unpredictable factors in determining how to make and use

the drug. These very necessary, but unpredictable factors are not taught in either the art or the specification for the specific administration of the compounds or DNAs for overexpression of Smad1 in vivo for disease treatment, the only intended use for the claimed method. Thus, Caldwell shows that in the absence of much additional information concerning in vivo effects, any agent that is found to increase the expression of Smad1 in vitro would be unpredictable when administered in vivo to affect the same biological process as seen in vitro.

3. State of the art. The arts of stimulating bone formation in an individual and regulating disease in an individual, at the time of the applicant's invention, were poorly developed. This is especially true with regard to the use of inducing a particular interaction by overexpression of Smad1 among the almost infinite number of different interactions in a large group of cells in a complex organism, such that a sufficient number of the correct cells (and not too many of the incorrect cells) are affected so as to have a significant effect on treating a disease by stimulating proper bone formation. The state of the arts of stimulating bone formation and regulating disease in an individual remain underdeveloped, and extensive unpredictable experimentation and discovery will be required before any successful reduction to practice is demonstrated for

even one of the methods encompassed by the claimed invention, let alone the broad scope, drawn to very different methods, encompassed by the claims.

4. Number of working examples. Applicants do not provide any working examples of the stimulation of bone formation in an individual, nor do they provide any working examples of the treatment of any disease in any individual or model organism. There aren't even prophetic teachings of how either of these goals might be achieved. In fact, applicants do not provide a prophetic teaching as to how they envision stimulating bone formation in an individual, as to how they envision regulating a disease, or even how regulation of that disease is to be specifically accomplished by increasing osteoblast differentiation and bone formation. The methods provide no steps that indicate how overexpression of Smad1 is to be achieved in osteoblast precursor cells in vivo, how tissue specificity is to be achieved, or even what dose of the inducer or DNA for overexpression is appropriate to effect the desired response.

5. Amount of guidance presented by applicants. Applicants present no actual or even prophetic guidance as how to their claimed invention could be practiced in humans or any other organism. A significant level of guidance in the specification

is necessary to enable one of ordinary skill in the art to practice the claimed invention due to the absence of such guidance in the art and the unpredictability in the art. If compounds are envisioned as inducers of overexpression of Smad1, then the various factors specific to the administration of each compound must be empirically determined, as discussed by Caldwell cited above. There are no teachings in the instant specification or the prior art regarding induction of a specific association between two proteins such as Smad1 and a transcription factor by overexpression of Smad1 as a means for stimulating bone formation. Although the instant specification demonstrates an induction of osteoblastic differentiation in vitro, no such demonstration is attempted in vivo, in any animal model. Such a demonstration would require unpredictable trial and error experimentation and would not be considered by one of skill in the art as routine, given the unpredictable parameters that must be determined for success in this complex area.

6. Scope of the claims. As indicated above, the claimed invention encompasses any method of inducing the interaction by overexpression of Smad1, including many very different compounds and method steps, each of which would have the unpredictability and the problems indicated above.

7. Level of skill in the art. The level of skill in the arts of stimulating bone formation in individuals and of regulating diseases in individuals is underdeveloped. The challenges, and the unpredictable ways of overcoming those challenges in various circumstances, that remain before gene therapy (which is encompassed by the elected method of overexpression of Smad1) is successfully reduced to routine practice are well documented, including by Anderson (4/30/98) and Verma et al (9/18/97), as are the challenges of appropriate tissue targeting using drugs (Langer) and formulating a bioactive compound into a drug that can be successfully administered to treat disease (Caldwell). Thus, the level of skill in the art of stimulating bone formation by inducing an interaction by overexpression of Smad1 (presumably by administering a compound) and using that induction to treat disease remains relatively low and underdeveloped.

Given the above analysis of the factors which the courts have indicated are critical in determining whether a given invention is enabled, it must be considered that the skilled artisan would have to practice undue and excessive unpredictable experimentation in order to practice the claimed invention given the complex nature of the invention, the high degree of unpredictability in the art, the underdeveloped state of the

art, the lack of working examples or art-recognized animal models showing induction of the claimed interaction to stimulate bone formation for treatment of disease, the complete lack of any real, specific guidance in the specification and the art, the broad scope of the claimed invention encompassing many different methods, and the underdeveloped skill in the art.

Response to Arguments

The applicant argues that the method of inducing osteoblast differentiation and bone formation has been described in detail and is fully supported by disclosure in Example 18 and Figure 7. This argument is not persuasive in overcoming the instant rejection because what is shown in Example 18 is one method of overexpressing Smad1 in vitro (by transfecting in vectors that overexpress Smad1) to induce osteoblast differentiation and mineralization. This is very different from the much more complex method instantly claimed: (any) method of overexpressing Smad1 in osteoblast precursor cells in an individual in order to stimulate osteoblast differentiation and bone formation (the only purpose of which is to treat unspecified bone diseases). The specification is totally lacking in any guidance concerning how to predictably accomplish overexpression of Smad1 in osteoblast precursor cells in an individual. The art of

converting an in vitro biological phenomenon to an in vivo treatment of disease, especially involving gene therapy or the use of unknown expression inducers is extremely unpredictable as shown by the art cited in the rejection above. Neither the art nor the specification teaches the necessary unpredictable details needed to be known before predictably performing the claimed method in individuals successfully. The applicant did not address these issues that are still applicable to the amended claims and thus the applicant's arguments are not persuasive in overcoming the instant rejection.

Claims 1 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record set forth in the paper mailed 10/22/03 (repeated below, slightly modified as necessitated by the applicant's amendment filed 6/1/04). Applicants' arguments filed 6/1/04 have been fully considered but they are not deemed to be persuasive.

The claimed invention is drawn to a method of stimulating bone formation in an individual comprising inducing an interaction between Smad1 and a homeobox-containing transcription factor (elected Hoxc-8) by overexpressing Smad1, wherein said interaction induces a BMP-responsive gene (elected osteopontin) which produces osteoblast and/or chrondroblast differentiation thereby stimulating bone formation. The claimed method reads on any method of overexpressing Smad1 in osteoblast precursor cells, which includes administration of compounds that cause overexpression of Smad1 (e.g., specific antisense molecules) and gene therapy to overexpress Smad1. The claimed invention is very broad genus of methods encompassing many very different methods of increasing expression of Smad1 with only the target, increasing the claimed interaction by increasing expression of Smad1, in common.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor

present in the claims is drawn to increasing expression of Smad1, which is actually just a description of the result to be achieved, without any description of the compounds or the method steps to achieve that effect. Beyond the fact that the claimed invention reads generally on administration of Smad1 nucleic acid or a compound to induce overexpression of Smad1, the specification fails to describe the structure of even one non-Smad1 nucleic acid which can be used to induce the overexpression of Smad1 as claimed. There is no description of what steps, compounds, or nucleic acids are to be used to overexpress Smad1 in vivo, so as to achieve any significant benefit. There is no description of the method steps to be performed in order to use Smad1 proteins or nucleic acids to induce the interaction as claimed in order to achieve a significant result.

Accordingly, in the absence of sufficient recitation of distinguishing characteristics of the compounds and methods to practice the claimed invention, the specification does not provide adequate written description of the claimed genus. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of compounds used to induce the overexpression as claimed, nor can the skilled artisan envision the specific method steps to practice the claimed invention, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification of the compounds to be used in the method steps. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016. Because the claimed methods appear to rely upon compounds to achieve the induction of the claimed interaction, the compounds themselves are needed for the claimed invention.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of

written description for that broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Response to Arguments

The applicant argues that in view of the disclosure of Example 18, the applicant submits that the specification has conveyed with reasonable clarity that the applicant was in possession of the claimed invention. This argument is not persuasive because the disclosure of Example 18 is drawn to the description of one particular in vitro method of overexpressing Smad1 in osteoblast cells in vitro. It is not a description of the method in an individual as claimed, let alone the description of other methods of overexpressing Smad1 such as by administration of (what particular?) compounds to individuals encompassed by the claimed method. The applicant did not address these issues that are still applicable to the amended claims and thus the applicant's arguments are not persuasive in overcoming the instant rejection.

Claims 1 and 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for reasons of record set forth in the paper mailed 10/22/03. Applicants' arguments filed 6/1/04 have been fully considered but they are not deemed to be persuasive.

The use of "Smad1" renders the claims vague and indefinite because the metes and bounds of the proteins encompassed by the term are unclear in light of the specification. The specification sets forth its own definition of Smad1: "As used herein, the term "Smad1" shall refer to any proteins that are homologous to Drosophila mothers against DPP or MAD protein." The metes and bounds of the proteins encompassed are unclear because there is no clear art-recognized definition of "homologous" in this context and the specification fails to set forth a clear indication of the metes and bounds of the term.

Response to Arguments

The applicant argues that it is well characterized that signal transduction in the TGF-beta superfamily is mediated by direct phosphorylation of Smad proteins including Smad1 and thus

one of ordinary skill in the art could readily recognize and distinguish the structure and function of Smad1, which was well known in the art. This argument is not persuasive because it does not address the basis of the rejection, that Smad1 is specifically defined in the specification in a way that is vague and indefinite, by defining Smad1 as referring to any proteins that are homologous to Drosophila mothers against DPP or MAD protein. It is this definition, which uses "homologous", for which there is no clear art-recognized definition in this context, that makes the term "Smad1" vague and indefinite. Which proteins are encompassed by homologous, and which proteins are not encompassed by homologous? The cited art and the applicant's arguments do not show that "homologous" in this context is not vague and indefinite.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

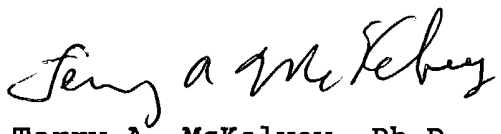
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (571) 272-0775. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

July 16, 2004